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HELLER EHRMAN LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CA 94025-3506

EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,951	AGUS ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	WAS

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37,39-52,54 and 55* is/are pending in the application.

4a) Of the above claim(s) *2-4,11,12,16-24,32-34,37,41-45,50,51 and 55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-10,14,15,25-31,35,36,39,40,46-49,52 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/11/2005; 5/31/2005; 2/3/2006; 8/23/2006.

DETAILED ACTION

Receipt is acknowledged of the papers filed 9/5/2006 in which claims 1-5, 11-13, 25, 29, 35-37 and 39-40 were amended; claims 38 and 53 were cancelled; and claim 55 was added. Claims 1-37, 39-52 and 54-55 are pending in the instant application. Claims 2-4, 11-12, 16-24, 32-34, 37, 41-45, 50-51 and 55 are withdrawn. Claims 1, 5-10, 14-15, 25-31, 35-36, 39-40, 46-49, 52 and 54 are under examination in the instant Office action.

Election/Restrictions

Claims 2-4, 11-12, 16-24, 32-34, 37, 41-45, 50-51 and 55 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/5/2006.

Applicant traversed the restriction requirement between Group I and Group II on the grounds that the search conducted for Groups I and II would be identical since the same gene must be searched for both groups.

Applicant's argument(s) have been carefully considered and are respectfully found unpersuasive. As set forth in the

requirement for election/restriction mailed 7/3/2006, the inventions of Group I and Group II are materially different in design, mode of operation and/or effect because the methods rely on chemically different and distinct biomarkers (nucleic acids in the case of Group I and proteins in the case of Group II). Furthermore the Group I and Group II methods differ in scope because the Group I inventions comprises isolating cellular RNA from a sample and quantifying the levels of transcript in the sample wherein the Group II invention comprises the use of immunohistochemistry or proteomics technology to determine the level of "transcript products" from a given sample. Moreover, the Group I and Group II inventions are not obvious variants because, for example, the determination of transcript levels as in Group I does not necessarily correlate with protein/transcript product levels as in Group II.

The restriction is still deemed proper and is therefore made FINAL.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR

1.821 through 1.825 because sequences are set forth in the specification that lack sequence identifiers (see, e.g., Tables 3 and 4). It is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 244.02). If the sequences are already present in the sequence listing, it would be remedial to amend the specification to include the appropriate sequence identifiers. Applicants are required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Specification

The disclosure is objected to because of the following informalities: sequences are set forth in the specification that lack sequence identifiers (see, e.g., Tables 3 and 4), see explanation, supra.

Appropriate correction is required.

Claim Objections

Claims 1, 5-10, 13-15, 35-36, 39-40, 46-50, 52 and 54 are objected to because of the following informalities: the claims are drawn to non-elected subject matter.

Claim 6 recites "[t]he method of claim 1 wherein said cancer is selected from the group consisting of ovarian cancer, colon cancer, pancreatic cancer, non-small cell lung cancer, breast cancer, and head and neck cancer" in lines 1-3 (emphasis added). Claim 6 is objected to because there is improper antecedent basis for "said cancer" in line 1. Does Applicant intend the cancer tissue sample recited in line 4 of claim 1, or did Applicant intend to provide antecedent basis for "cancer" in some other portion of the claim?

Similarly, claims 29 and 30 recite "the cancer" when referring to "cancer tissue" in claim 25. Does Applicant intend the cancer tissue recited in line 3 of claim 25, or did Applicant intend to provide antecedent basis for "cancer" in some other portion of the claim?

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5, 15, 35, 39 & 54, and therefore dependent claims 6-10, 13-14, 36, 40, 46-49 & 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "[a] method for predicting the likelihood that a patient who is a candidate for treatment with an EGFR inhibitor will respond to said treatment, comprising determining the expression level of a prognostic RNA transcript or its expression products in a cancer tissue sample obtained from said patient, wherein the prognostic transcript is the transcript of AREG, wherein over-expression of the transcript of AREG or the corresponding expression product, indicates that the patient is not likely to respond well to said treatment" in lines 1-14 (emphasis added).

Claim 1 is vague and indefinite in that the metes and bounds of "over-expression" are unclear. Applicant defines "over-expression" with regard to an RNA transcript as "the level of the transcript determined by normalization to the level of reference mRNAs, which might be all measured transcripts in the specimen or a particular reference set of mRNAs (see page 7,

paragraph [0024]). What level of expression is required for over-expression: e.g., any level above a normalized level of transcript or any level simply determined by normalization to the level of any given reference mRNA?

Furthermore, the terms "not likely" and "well" in claim 1 are relative terms which render the claim indefinite. The terms "not likely" and "well" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. For example, does Applicant intend that in order for a patient to respond well to a treatment, the patient must make a full recovery or simply that the patient survives? Is anything greater than a 51% chance that patient will not respond well, make it "not likely" that the patient will not respond well, or is likelihood based upon some other standard?

Similarly, claim 5 recites "[t]he method of claim 1 wherein over-expression is determined relative to the mean level of the RNA transcript or the product of two of more reference genes" in lines 1-4 (emphasis added). Claim 5 is vague and indefinite in that the metes and bounds of over-expression are unclear as explained for claim 1, supra. What level of expression is required for over-expression: e.g., any level above a

normalized level of transcript or any level simply determined by normalization to the level of any given reference mRNA?

Claim 15 recites "[t]he method of claim 1, wherein the EGFR inhibitor is a small molecule" in line 1 (emphasis added). Claim 1 is vague and indefinite in that it is unclear what Applicant intends by a "small" molecule. Does Applicant intend to refer to a class of molecules within a given size range, or does Applicant intend, for example, any molecule which is not an antibody or peptide or DNA fragment, i.e. a particular class of molecules?

Claim 35 recites "[a] prognostic method comprising: (a) subjecting a sample comprising cancer cells obtained from a patient to quantitative analysis of the expression level of the RNA transcript of AREG, or its products, and (b) identifying the patient as likely to have a decreased likelihood of responding well to treatment with an EGFR inhibitor if the normalized expression levels of said RNA transcript or its products, are elevated above a defined expression threshold" in lines 1-9 (emphasis added). Claim 35 is vague and indefinite in that the term "well" is a relative term which renders the claim indefinite. The term "well" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not

be reasonably apprised of the scope of the invention. For example, does Applicant intend that in order for a patient to respond "well" to a treatment, the patient must make a full recovery or simply that the patient survives?

Claim 39 recites "[t]he method of claim 35 or 37 wherein the levels of the RNA transcripts of said genes are normalized relative to the mean level of the RNA transcript or the product of two or more reference genes" in lines 1-3 (emphasis added). Claim 39 is vague and indefinite in that it is unclear which cells are used to determine the "mean level of the RNA transcript," i.e., is the mean level of the RNA transcript determined from a similar, non-cancerous cell, a precancerous cell or some other cell or tissue type?

Claim 54 recites "[a] kit comprising one or more of (1) extraction buffer/reagents and protocol; (2) reverse transcription buffer/reagents and protocol; and (3) qPCR buffer/reagents and protocol suitable for performing the method of any one of claims 1, 35 and 37" in lines 1-3 (emphasis added). Claim 54 is vague and indefinite in that it is unclear which reagents are "suitable for performing the method of any one of claims 1, 35 and 37" as recited in line 3. Does Applicant intend reagents such as primers and microarrays for specific AREG sequences or for hybridization of the encompassed

nucleic acids, or does Applicant intend reagents limited to buffers and enzymes?

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-10, 13-15, 25-31, 35-36, 39-40, 46-49, 52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn broadly to methods for predicting the likelihood that a patient will respond to treatment with an EGFR inhibitor, wherein over-expression of any AREG transcript is indicative that the patient will have a decreased likelihood of responding well to a treatment with an EGFR inhibitor as well as kits suitable for such methods. Some claims are further drawn to such methods wherein the cancer is selected from the group

consisting of ovarian cancer, colon cancer, pancreatic cancer, non-small cell lung cancer, breast cancer, and head and neck cancer. Some claims are further limited to EGFR inhibitors which are antibodies, antibody fragments or small molecules. The claims do not provide any structural information with regard to the AREG sequences/EGFR inhibitors or cancer tissue samples capable of use in such methods such that AREG over-expression is indicative that a patient with cancer will be less likely to respond to treatment with any EGFR inhibitor. Thus, the rejected claims comprise a set of nucleic acid sequences/cancer tissue samples and EGFR inhibitors that are defined by their function in the method.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification teaches that there are several EGFR inhibitors "such as ZD1839 (also known as gefitinib or Iressa); and OSI774 (Erlotinib, Tarceva™)" which are promising drug candidates for the treatment of cancer (see page 17, paragraph [0059]). As its sole example

of a method for predicting the likelihood that a candidate patient will not respond to an EGFR inhibitor, comprising determining the over-expression of AREG wherein AREG over-expression is indicative that a patient is not "likely" to respond "well" to said treatment, the specification teaches the results of a Phase II clinical study of gene expression in tissue samples obtained from 17 human patients with non-small cell lung cancer (NSCLC) who responded or did not respond to treatment with one unspecified EGFR inhibitor (see, e.g., page 2, paragraph [0008]; page 19, paragraph [0068]-[0069]; and page 21, paragraph [0078]). Expression analysis was performed on mRNA transcripts of 185 cancer-related genes and 7 reference genes (see, e.g., page 20, paragraph [0074]). The specification emphasizes that while the data presented are from tissue samples from NSCLC, the conclusions drawn from the tissue expression profiles are equally applicable to other cancers, including colon cancer, ovarian cancer, pancreatic cancer, breast cancer and head and neck cancer (page 23, paragraph [0085]).

The specification does not teach that AREG is overexpressed in any of the samples tested.

The specification does not teach which AREG sequences (including mutants, allelic and splice variants, etc.) can be used in such a method.

The specification does not teach the EGFR inhibitors to which a patient would have a decreased likelihood of responding should normalized AREG expression be above a "defined expression threshold."

No description is provided of samples other than paraffin-embedded, fixed tissue samples of non-small cell lung cancer patients used in such methods.

Even if one accepts that the example described in the specification meets the claim limitations of the rejected claims with regard to structure and function, the example is only representative of one unspecified EGFR inhibitor from one type of cancer tissue sample which was assessed for AREG sequences which can be amplified with the disclosed primers. The results are not necessarily predictive of any other EGFR inhibitor, any other cancer tissue samples or any other AREG sequences. Thus it is impossible to extrapolate from the example described herein those nucleic acid molecules/EGFR inhibitors/cancer tissue samples that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe a set of EGFR inhibitors/AREG nucleic acids/cancer tissue samples that can be used in a method for determining likelihood that a

patient will respond to treatment with the EGFR inhibitor based upon a determination of AREG over-expression. For example, the genus of EGFR inhibitor drugs is very large. In an article published post-filing Giaccone et al teach at least six EGFR inhibitors: Iressa, Tarceva, lapatinib, cenertinib, ZD6474, and AEE788 (*Nature Clinical Practice Oncology* **2**:(11)554-561, 2005; see entire document, especially the Introduction). Giaccone et al teach that each of these drugs works differently or has a different spectrum of EGFR targets. For example, Iressa and Tarceva inhibit the tyrosine kinase activity of EGFR by competing with ATP for the ATP binding site, lapatinib and canertinib have activity on more members of the ErbB family, and ZD6474 and AEE788 inhibit the vascular endothelial factor receptor in addition to EGFR (ibid).

Given the very large genus of AREG nucleic acid molecules/EGFR inhibitors/cancer tissue samples encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to nucleic acids/inhibitors/cancer tissue samples capable of fulfilling the claim limitations of claims 1, 5-10, 13-15, 25-31, 35-36, 39-40, 46-49, 52 and 54, the skilled artisan would not have been able to describe the broadly claimed genus of AREG sequences/cancer tissue samples that are indicative (when over-expressed in a

candidate patient with cancer) of a decreased likelihood that said patient will respond well to any EGFR inhibitor. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those nucleic acid sequences, cancer tissue samples and EGFR inhibitors that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 1, 5-10, 13-15, 25-31, 35-36, 39-40, 46-49, 52 and 54.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-10, 13-15, 25-31, 35-36, 39-40, 46-49,52 and 54 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. The specification does not reasonably provide enablement for methods wherein over-expression of any AREG transcript indicates that a patient is not likely to respond well to treatment with any EGFR inhibitor.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention:

The claims are drawn broadly to methods for predicting the likelihood that a patient will respond to treatment with an EGFR inhibitor, wherein over-expression of any AREG transcript is indicative that the patient will have a decreased likelihood of responding well to said treatment as well as kits suitable for such methods. Some claims are further drawn to such methods wherein the cancer is selected from the group consisting of ovarian cancer, colon cancer, pancreatic cancer, non-small cell lung cancer, breast cancer, and head and neck cancer. Some claims are further limited to EGFR inhibitors which are

antibodies, antibody fragments or small molecules. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)). The nature of the invention is complex in that over-expression of a single gene from any given cancer tissue sample is used to determine whether a patient is likely to respond to any given EGFR inhibitor, a molecule which does not necessarily act upon the AREG gene product itself.

Breadth of the Claims:

The claims are drawn broadly to methods for predicting the likelihood that a patient will respond to treatment with any EGFR inhibitor by determining the level of any AREG transcript in any cancer tissue sample, wherein over-expression or normalized expression of AREG above a "defined expression threshold" indicates that the patient has a decreased likelihood of responding well to said treatment. The term "EGFR inhibitor" is broad in that it includes every inhibitor in the class of EGFR inhibitors as well as molecules which inhibit EGFR indirectly (see definition at page 9, paragraph [0035]). Any AREG nucleic acid is encompassed, including naturally and non-naturally occurring allelic, mutant, and splice variants.

Furthermore, any cancer tissue sample from any candidate patient may be utilized.

Guidance Provided by the Specification:

The specification teaches that the present invention is based on the finding of a Phase II clinical study of gene expression in tissue samples obtained from 17 human patients with non-small cell lung cancer (NSCLC) who responded or did not respond to treatment with one unspecified EGFR inhibitor (see, e.g., page 2, paragraph [0008]; page 19, paragraph [0068]-[0069]; and page 21, paragraph [0078]). Expression analysis was performed on mRNA transcripts of 185 cancer-related genes and 7 reference genes (see, e.g., page 20, paragraph [0074]). All samples were from patients that had a history of prior treatment for NSCLC (page 20, line 1). Of the 185 cancer-related genes tested, 23 were found to have p-values of <0.10 between 15 non-responders and 2 responders (page 21, paragraph [0078] and page 22, Table 1). The specification teaches on page 22, paragraph [0080] that elevated expression of other genes such as STAT5A, STAT5B, WISP1, CKAP4, FGFR1, cdc25A, RASSF1 or ErbB3 in a tumor is an indication that the patient is not likely to respond well to treatment with an EGFR inhibitor. The specification emphasizes that while the data presented are from tissue sample from NSCLC, the conclusions drawn from the tissue expression

profiles are equally applicable to other cancers, including colon cancer, ovarian cancer, pancreatic cancer, breast cancer and head and neck cancer (page 23, paragraph [0085]).

The specification does not teach that AREG is over-expressed in any of the samples tested.

The specification does not teach the EGFR inhibitors to which a patient would have a decreased likelihood of responding should normalized AREG expression be above a "defined expression threshold."

Accordingly the specification is not enabled for determining the normalized level of AREG in any given cancer tissue sample wherein an increase in AREG is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor. The specification also does not provide an example for determining the normalized level of a representative number of corresponding gene products of AREG in cancer tissue samples wherein an increase in AREG expression is indicative that the patient will show a decreased likelihood of response to treatment with an EGFR inhibitor.

State of the Art:

The state of the art at the time of Applicant's filing was underdeveloped with regard to the use of prognostic markers generally, as well as with regard to the specific use of any

AREG transcript to predict that a patient with any given cancer will have a decreased likelihood of responding to an EGFR inhibitor. Kanters et al (*European Respiratory Journal* **8**:1389-1397, 1995) teach a number of prognostic factors for NSCLC (AREG is not mentioned) as well as considerations necessary to make prognostic markers successful in determining survival and treatment outcome. Among the considerations to be made are such factors as whether or not the prognostic factor is specific for a tumor cell or whether the marker merely represents enhanced expression of a naturally occurring product (see page 1395, first column, first full paragraph). Also, to weigh the importance of a prognostic marker it must be determined if the marker is a truly independent predictor of outcome, i.e. "prospective studies are needed with sufficient number of patients to compare a panel of determinants of outcome of treatment in a statistically sound way" (page 1395, 1st column, 2nd full paragraph; emphasis added). In the instant case, Applicant has only tested one EGFR inhibitor against a panel which includes 17 patients, only 2 of whom did not respond to treatment with the EGFR inhibitor. Applicant has not determined that AREG or any other differentially expressed gene is determinative of likelihood of response to EGFR inhibitors

generally or to the utilized (albeit undisclosed) EGFR inhibitor specifically.

Fontanini et al teach the use of prognostic markers which include AREG (*Clinical Cancer Research* **4**:241-249, 1998; see entire document). However, Fontanini et al also teach that the potential prognostic role of such genes as AREG as well as TGFα, EGFR and erbB-2 which were investigated in human NSCLC pilot studies provide "no conclusive information on the prognostic impact of these biological parameters" (see page 245, 2nd column, first full paragraph). Thus, neither the specification nor the art of record has established a nexus between AREG expression levels and response to EGFR inhibitors. The specification teaches that in addition to AREG, 6 genes correlated with clinical benefit of EGFR treatment with a $p<0.1$ and these genes did not include AREG (see page 23, paragraph [0082] and Table 2). These other six genes are therefore potentially even MORE likely to indicate whether a patient is not likely to respond to an EGFR inhibitor. Neither the specification nor the art of record havè demonstrated that AREG overexpression is necessary or even sufficient to determine whether a patient responds to an EGFR inhibitor. Given the above, one of ordinary skill in the art could not predict based upon the evidence presented, that by determining the level of expression of an AREG transcript one

could determine the likelihood of a decreased response to an EGFR inhibitor.

The unpredictability of correlating gene expression level to any phenotypic quality is taught in the prior art by Wu (*J. Pathol.* **195**(1):53-65, 2001). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics" informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 - Discussion). Additionally, post-filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, page 20, Dec. 20, 2004) teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study

will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (middle column, 1st full paragraph).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels. Chen et al (*Molecular and Cellular Proteomics* **1**:304-313, 2002) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pages 311-312).

The Predictability or Unpredictability of the Art and Degree of Experimentation:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention

without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. The more that is known in the prior art about the nature of the invention, how to make and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling.

In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach which EGFR inhibitors were used in the working example. The specification does not teach a representative number of EGFR inhibitors. Furthermore, the specification does not teach a representative number of AREG gene products or cancer tissue samples for which such a method can be performed. Accordingly, although the level of skill in the art of molecular

biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require a great amount of undue and burdensome experimentation for one of ordinary skill in the art to make and use the invention as claimed. One of ordinary skill in the art would first need to validate AREG as a marker against a panel of other potential markers and then determine which EGFR inhibitors could be used in the claimed methods such that over-expression of AREG was determinative of decreased likelihood of response to the inhibitor. Such undue experimentation is exacerbated by the breadth of the claims which would require one of ordinary skill in the art to determine in which cancer tissue samples/patients such a prediction could be made in combination with which functional AREG transcript sequences and EGFR inhibitors.

Conclusion

No claim is allowed.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If

Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

November 22, 2006

NANCY VOGEL
PRIMARY EXAMINER